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10/648,593	08/26/2003	Fei Huang	D0273 NP	5265

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/648,593	HUANG ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 September 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0507;1207*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response on December 7, 2007, to the Action on the Merits of this case mailed August 8, 2007, is acknowledged. It is acknowledged that applicants have cancelled Claims 42-51 and amended Claim 41. Claim 41 is pending and is hereby reconsidered.

Drawings-Objections

Applicants' replacement drawings, filed September 14, 2006, are acknowledged.

Figures 1 and 7 of said replacement drawings are objected to because neither the figures nor the legends thereto explain the meaning of the black squares in the figures.

Figure 1 is further objected to because the legend thereto states: "The cell lines labeled...in blue are classified as sensitive to BMS-A"; however, there is no blue color in Figure 1. Moreover, the title of the figure indicates that the data represent polynucleotide expression patterns, not sensitivity to BMS-A.

Figure 1 is further objected to because the brackets at the top, linking cell lines, are not explained.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

Provisional rejection of Claim 41 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 16 of US Application 11/072,175, for the reasons set forth in the prior actions, is withdrawn because Claim 16 has been cancelled. However, Claim 41 is herein provisionally rejected under the judicially created doctrine of

obviousness-type double patenting as being unpatentable over Claims 21 and 23-28 of US Application 11/072,175, for the same reasons previously explained for Claim 16 therein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons.

Claim 41 recites a method wherein identifying a breast cancer cell as being sensitive or resistant to a tyrosine kinase inhibitor is determined by comparing the expression of specific gene(s) "relative to a standard" (lines 5 and 7). However, neither the claims nor the specification define what said "standard" is. The metes and bounds of the recited invention are unclear.

Claim 41 recites the phrase "determining the expression profile of a gene expression product from at least one informative gene in a sample, wherein said at least one informative gene is EphA2". It is unclear from said phrase whether the method encompasses (i) determining the expression profile of only the EphA2 gene and from the expression profile of EphA2 gene products, predicting sensitivity/resistance to the inhibitor or (i) determining the expression profile of a population of genes, wherein EphA2 is one gene of the population, and from the expression profile of said population of genes, predicting sensitivity/resistance to the inhibitor. The skilled artisan would not know the metes and bounds of the invention. For purposes of examination, it is assumed that said phrase means determining the expression profile of a

population of genes, wherein EphA2 is one gene of the population, and from the expression profile of said population of genes, predicting sensitivity/resistance to the inhibitor.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Rejection of Claim 41 under 35 U.S.C. 112, first paragraph/lack of enablement, for the reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(A) The claimed invention is enabled by the specification as filed as well as the Declaration filed by Dr. Huang on September 14, 2006.

(B) The rejection based on prediction for "any breast cancer cell" is in error, as this basis for rejection was withdrawn by the action of December 19, 2006 (pg 5).

(C) The burden of establishing that undue experimentation is required to practice the invention has not been met.

(D) EphA2 expression is a reliable predictor of whether a breast cancer cell is sensitive or resistant to a protein kinase inhibitor. See Dr. Huang's declaration.

(E) Rejection based on a "genus of cell lines" or a "genus of compounds" is not consonant with the instant invention, which is a diagnostic method of predicting which cells are sensitive or resistant to a protein kinase inhibitor.

(F) The Examiner appears to believe that the instant invention is based on testing the effects of inhibitors on breast cancer cells; but, it is not so directed. The instant invention is directed to a diagnostic method for predicting which breast cancer cells are sensitive or resistant to a protein kinase inhibitor by assaying EphA2 levels.

(G) Claim 41 has been amended to remove the "one or more" language.

(H) Neither Zelinski et al nor Carles-Kinch et al teach the use of the method currently claimed.

These arguments are, or not, found to be persuasive for the following reasons.

(A) Reply: The instant invention is direct to a method of predicting whether any breast cancer cell, including cells from a patient, will be sensitive or resistant to any protein tyrosine kinase inhibitor that directly or indirectly inhibits the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2, by assaying the levels of any population of gene products, wherein the population comprises EphA2.

The specification is enabling for determining the sensitivity (IC_{50}) of a panel of 23 breast cancer cell lines to BSM-A, calculating the $\log_{10}IC_{50}$ for each cell line, calculating the mean $\log_{10}IC_{50}$ for the panel of cell lines, and, based on said mean, arbitrarily dividing said panel of cell lines in to sensitive (below the mean) and resistant (above the mean). The specification also is enabling for using hybridization methods to assess the relative expression of EphA2-encoding mRNA in said panel of breast cancer cell lines (parg bridging pg 105-106), calculating the median expression of EphA2-encoding mRNA for said 23 cell lines, and, based on said median, arbitrarily dividing said panel of cell lines into those having expression greater than the median and those having expression less than the median (Fig. 1). Using the above arbitrary division of

said panel of 23 breast cancer cell lines, the specification is enabling for analyzing for a correlation between expression levels of EphA2-encoding mRNA and sensitivity/resistance to BSM-A for (Fig 1, gene 1, vs Table 1). Assuming the black squares on the right (red) side of Fig 1 represents high expression, the number of cell lines in which sensitivity to BSM-A correlates with EphA2 expression is 17/23 = 74% (none of the BT549, HCC38, MDA-MB-468, MDA-MB-436, or MDA-MB-435 cell lines showed such a correlation). However, the specification does not reasonably provide enablement for any method of predicting whether any breast cancer cell will be sensitive or resistant to any protein tyrosine kinase inhibitor that directly or indirectly inhibits the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2, by assaying the levels of any population of gene products, wherein the population comprises EphA2.

The specific reagents and steps used for any method determine the method's success. Predictability of which steps and reagents can be used to obtain the desired effect requires a knowledge of, and guidance with regard to how said steps and reagents relate to the desired outcome. In the instant case, the skilled artisan must be provided guidance as to how any population of gene products comprising EphA2 can be used to predict the sensitivity/resistance of any breast cancer cell to essentially any protein tyrosine kinase inhibitor. However, this case is limited to correlating the expression of EphA2 to sensitivity/resistance to BMS-A in a single panel of 23 breast cancer cell lines.

Methods for analyzing expression of gene products as well as testing sensitivity to protein kinase inhibitors are known in the art. However as recently as 2007, the use of gene product expression profiling for predicting the responsiveness of breast cancer cells to any

specific compound was unpredictable (Gruvberger-Saal et al, 2006, pg 1021-1023; Sotiriou et al, 2007, pg 550-551). The specification fails to provide evidence as to which of the essentially unlimited number of panels of gene products comprising EphA2 can be used to successfully predict the sensitivity of any breast cancer cell line to any protein kinase inhibitor. In fact, Applicants' declaration of September 2006 provides evidence that analysis of genes, in addition to EphA2, reduces the predictability of the recited method (Exhibits G-K). In the absence of guidance as to which populations of genes to use, the skilled artisan is reduced to the undue burden of analyzing the expression of any population of gene products, testing the sensitivity to any protein kinase inhibitor, and determining which genes can be used to predict sensitivity/resistance to any said kinase inhibitor. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification.

The specification does not support the broad scope of Claim 41 which, encompasses all methods of predicting whether any breast cancer cell will be sensitive or resistant to any protein tyrosine kinase inhibitor that directly or indirectly inhibits the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2, by assaying the levels of any population of gene products, wherein the population comprises EphA2. The specification does not support the broad scope of Claim 41 because the specification does not establish: (A) a standard by which to compare whether the EphA2 gene product, or any other specific gene product, is "increased" or "decreased" in any specific breast cancer cell; (B) a standard by which to

determine whether a specific breast cancer cell is sensitive or resistant to any specific protein tyrosine kinase inhibitor; (C) a correlation between expression of EphA2-encoding mRNA and sensitivity to BMS-A in any population of breast cancer cells other than the one population disclosed in the specification; (D) a correlation between expression of any EphA2 polypeptide to be assayed, or any other polypeptide, and sensitivity to any encompassed tyrosine kinase inhibitor; (E) a correlation between expression of any possible encompassed gene product to be assayed and sensitivity to any encompassed tyrosine kinase inhibitor; (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices of populations of gene products can be successfully analyzed to predict the sensitivity/resistance to the essentially infinite possible choices of protein tyrosine kinase inhibitors in any breast cancer cell.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of methods to predict whether any breast cancer cell will be sensitive or resistant to any protein tyrosine kinase inhibitor that directly or indirectly inhibits the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2, by assaying the levels of any population of gene products, wherein the population comprises EphA2. Without sufficient guidance, determination of the identity of methods having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

(B) Reply: It is acknowledged that this basis for the rejection was withdrawn, as the objective of the method is to predict which cells are sensitive/resistant to a protein tyrosine kinase inhibitor. Nonetheless, it is noted that, since the specification fails to provide guidance as to which population of cells are likely to be successfully analyzed with the recited method, analyzing any breast cancer cell, contributes to the broad scope of the invention.

(C) Reply: See (A) above.

(D) Reply: It is acknowledged that the specification discloses that, in a single population of 23 breast cancer cell lines, above the median EphA2 expression (Fig 1) correlated with above the mean sensitivity of to a single protein tyrosine kinase inhibitor, BSM-A (Table 2). It is also acknowledged that Dr. Huang's declaration asserts that EphA2 expression correlated with sensitivity/resistance of the same population of cell lines to the BSM variants, BSM-B, BSM-C, BSM-D, and BSM-E (Exhibits H-K). However, said evidence is not sufficient to convince the skilled artisan that, more likely than not, EphA2 expression correlates with sensitivity/resistance of all breast cancer cells to any protein tyrosine kinase inhibitor that directly or indirectly inhibits the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2.

(E) Reply: It is acknowledged that the invention is directed to a method of predicting which breast cancer cells are sensitive or resistant to a protein kinase inhibitor; the invention is not directed to a cell line or a compound. However, the invention encompasses predicting whether any cell, encompassed by the genus of any breast cancer cell, is sensitive/resistant to any compound, encompassed by the genus of any protein tyrosine kinase inhibitor that directly or indirectly inhibits the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-

Kit, and EphA2. For the full scope of the invention to be enabled, the skilled artisan must be able to use the recited method to predict which of said genus of cells are sensitive, and which are resistant, to which of said genus of compounds. In addition, the genus of compounds is not a fixed genus; what is known to be the genus of protein tyrosine kinase inhibitors that directly or indirectly inhibits the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2 changes over time. Clearly, the specification fails to teach which populations of gene products can be used to predict sensitivity/resistance to protein tyrosine kinase inhibitors that were not known at the time of filing.

(F) Reply: It is acknowledged that the instant invention is directed to a diagnostic method for predicting which breast cancer cells are sensitive or resistant to a protein kinase inhibitor by assaying EphA2 receptor levels.

(G) Reply: It is acknowledged that Claim 41 has been amended to remove the "one or more" language in regards to the specificity of the protein tyrosine kinase inhibitor. However, the specification fails to limit the genus of protein tyrosine kinase inhibitors encompassed by the instant invention as those that directly inhibit the specific kinases recited in Claim 41. In fact, the specification states:

> "Such marker polynucleotides encompass the above-listed protein tyrosine kinase-encoding polynucleotides, and serve as useful molecular tools for predicting a response to drugs, compounds, biological agents, chemotherapeutic agents, and the like, preferably those drugs and compounds, and the like, that affect protein tyrosine kinase activity **via direct or indirect inhibition** or antagonism of the protein tyrosine kinase function or activity." (Examiner's emphasis).

Clearly, the genus of inhibitors that affect, either directly or indirectly, the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2 is a large genus of inhibitors. The specification has failed to enable the skilled artisan to predict, by assaying

EphA2 levels, which breast cancer cells will be sensitive or resistant to said very large genus of inhibitors.

(H) Reply: It is acknowledged that neither Zelinski et al nor Carles-Kinch et al teach use of the method currently claimed; the methods of Zelinski et al Carles-Kinch et al examine the effects of treatment, not prediction of sensitivity.

Written Description

Rejection of Claim 41 under 35 U.S.C. 112, first paragraph/written description, for the reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments. There is sufficient description provided by the specification as filed, as well as the Declaration filed by Dr. Huang on September 14, 2006, to establish that Applicants were in possession of the claimed invention. Specifically, EphA2 was identified as being the top predictor out of all 137 predictor genes outlined in Table 2, which lists EphA2 a being highly expressed in sensitive breast cancer cells and lists EphA2 as being inhibited by BMS-A (Table 2, gene 1). Thus, the specification demonstrates that sensitive cells having increased expression of EphA2, which correlates with an effect of the inhibitor to reduce growth.

These arguments are not found to be persuasive for the following reasons. It is acknowledged that Applicants were in possession of a method whereby analysis of EphA2 expression levels in a single population of breast cancer cells to correlate sensitivity of the cells to BMS-A and specific variants thereof. However, said example does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of a method for predicting whether any breast cancer cell will be sensitive or resistant

to any protein tyrosine kinase inhibitor that directly or indirectly inhibits the activity of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, and EphA2, by assaying the levels of any population of gene products, wherein the population comprises EphA2. Given this lack of description of representative species encompassed by the genera of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim 41 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. Claim 41 introduces the limitation of comparing the expression of a gene product "relative to a standard". The specification fails to describe said limitation and, thus, Claim 41 is rejected under 35 U.S.C. 112, first paragraph, for introducing New Matter.

Allowable Subject Matter

No claims are allowable.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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